REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 1, 4, 6-9, 13, 16, 17, 19, 20, and 22-27 will be pending in the application. Claims 1, 4, 6-9, 16, 19 and 20 are amended, claims 2, 3, 5, 10, 18, and 21 are canceled, and new claims 23-27 are added.

Claim 1 has been amended to delete the process limitations of the claim, which have been incorporated into new claim 25. Support for the amendments to claim 1 can be found in the specification at, *e.g.*, paragraphs 0010 and 0011. Reference to the specification herein refers to the published application (US 2006/0142220 A1). Claim 4 is amended to be consistent with the amendments to independent claim 1. Claim 6 is amended to modify the claim dependency in view of the cancelation of claim 5. Claims 7 and 8 have been amended to depend from new claim 25, and support for the amendments can be found in the specification at, *e.g.*, paragraphs 0010 and 0011. Claim 9 is amended to be consistent with the addition of new claim 25, from which it now depends. Support for the amendment to claim 16 can be found in the specification at, *e.g.*, paragraphs 0010, 0012 and 0013. Claims 19 and 20 are amended to modify the claim dependency in view of the cancelation of claim 18. Support for new claim 23 can be found in the specification at, *e.g.*, paragraphs 0018 and 0038. Support for new claim 24 can be found in the specification at, *e.g.*, paragraph 0038. Support for new claim 25 can be found in the specification at, *e.g.*, paragraphs 0010, 0011 and 0013. Support for new claim 26 can be found in the specification at, *e.g.*, paragraph 0017. Support for new claim 27 can be found in the specification at, *e.g.*, paragraph 0013.

The amendment of claims herein should not be construed as an acquiescence to any position taken by the Examiner with respect to the scope of the originally-filed or previously pending claims. Rather, Applicants have amended the claims to advance prosecution of the application. No new matter is added by the present amendment.

Interview Summary

Applicants thank the Examiner for taking time to discuss the present office action with the undersigned on October 8, 2009, in which both the enablement and obviousness

rejections were discussed, as well as proposed claim amendments. Although no formal agreement was reached, Applicants respectfully request favorable reconsideration of the outstanding rejections based on the presently amended claims and the remarks set forth below.

Claim Rejections - 35 U.S.C. §112, 1st Paragraph - Enablement

Claims 1-10, 13 and 16-22 are rejected under 35 U.S.C. 112, 1st paragraph because the specification allegedly does not enable changing the circulatory half-life of recombinant human C1 inhibitor or other glycoproteins by O-linked carbohydrate modification via the use of any enzyme other than ST3Gal I or ST3Gal III. In particular, the Examiner states that the specification only provides guidance regarding a method of using a C1 inhibitor that is sialylated on O-linked carbohydrate moieties *in vitro*. Further, the Examiner states that the art is unpredictable with respect to the function of various carbohydrates in glycoproteins, and that different glycosylation moieties introduced by different enzymes may cause various effects apart from increasing circulatory half-life, which would require the skilled artisan to experiment unduly to make and use the full scope of the claimed invention. *See* pp. 4-5 of the Office Action.

Without agreeing with the Examiner's position, Applicants have amended independent claims 1 and 16 to refer to specific modifications. Newly added claim 25 also recites specific modifications to the C1 inhibitor. Claim 1 has been amended to recite a recombinant human C1 inhibitor having a modified O-linked carbohydrate comprising a sialylated terminal galactose residue, while claim 16 has been amended to indicate that the non-sialylated O-linked carbohydrate removed by the enzyme(s) comprises a terminal galactose residue. New claim 25 recites use of a sialyltransferase capable of sialylating a terminal galactose residue. Moreover, the methods recited in claim 16 and new claim 25 refer to *in vitro* modifications. Thus, Applicants submit that the presently claimed invention is fully enabled by the specification.

The Enzymes of the Claimed Invention Produce Predictable Modifications

The specification clearly teaches that capping or removal of terminal galactose residues on O-linked carbohydrates interferes with glycoprotein binding to receptors involved in clearance and results in a prolonged circulatory life-time in the blood. *See* paragraph 0010.

Suitable enzymes include, for example, sialyltransferases for capping terminal galactose residues, galactosidases for removing terminal galactose, and endo-acetylgalactosaminidases for hydrolyzing the covalent linkage between the polypeptide and galactosamine of non-sialylated structures. *Id.* In each of these cases, the number of exposed O-linked galactose residues is reduced and the circulatory life-time of the glycoprotein is enhanced. *Id.*

Examples 1-3 of the specification discuss *in vitro* sialylation of recombinant human C1 inhibitor with sialyltransferases ST3Gal III and ST3Gal I, and the pharmacokinetics of the modified proteins in rats. As discussed and illustrated in Example 3 (see, *e.g.*, Table 5), the plasma circulatory half-life of the modified proteins was significantly enhanced as compared to the unmodified recombinant protein. Moreover, the results clearly show that the extended circulatory half-life is the result of O-linked carbohydrate modification. *See* paragraph 0037.

Applicants submit that although only sialyltransferases ST3Gal III and ST3Gal I are exemplified in the specification, a skilled artisan would be capable of using any sialyltransferase capable of sialylating a terminal galactose residue to carry out the full scope of the invention recited in independent claim 25. A number of other sialyltransferases, whose substrates are the same as those for ST3Gal III and ST3Gal I, were known in the art as of the priority date of the present application. As discussed in the response of July 7, 2008, Harduin-Lepers *et al.*, *Glycobiology* 5(8):741-758 (1995), and Harduin-Lepers *et al.*, *Biochimie* 83:727-737 (2001) report a number of cloned and characterized sialyltransferase enzymes that perform the same functions as ST3Gal III and ST3Gal I. Based on the specification, the skilled artisan could readily identify other sialyltransferases to use in the presently claimed invention in addition to ST3Gal III and ST3Gal I, and would expect the same modifications to be produced in the recombinant human C1 inhibitor by *in vitro* incubation with the enzyme(s). Because the same modifications occur, the physical properties of the protein would not be different from those produced by the enzymes discussed and exemplified in the specification, and the skilled artisan would not be required to experiment unduly, if at all, to practice the full scope of the invention recited in independent claim 25. Thus, the full scope of the invention recited in independent claim 25 is enabled by the specification.

The composition recited in independent claim 1 is enabled by any method of making the composition. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. §112 is satisfied. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. §112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 3 USPQ2d 1737, 1743 (Fed. Cir.), *cert denied*, 484 U.S. 954 (1987). In view of the exemplified embodiments discussed in Examples 1-3, Applicants submit that the full scope of the invention recited in independent claim 1 is enabled by the specification.

Similarly, Example 4 of the specification discusses *in vitro* removal of non-sialylated O-linked carbohydrates comprising a terminal galactose residue from recombinant human C1 inhibitor with Endo-α-N-Acetylgalactosaminidase. As reported in paragraph 0038, the modified protein had a significantly reduced amount of Galβ1,3GalNAc. Although the pharmacokinetics of this particular modified glycoprotein are not discussed, the specification makes clear that removal of terminal galactose residues, as reported in Example 4, leads to a prolonged circulatory life-time in the blood. *Supra*. The Examiner has provided no argument or evidence to dispute the veracity of the claims made in the specification with regard to the correlation between O-linked terminal galactose residues and the circulatory half-life of glycoproteins, particularly in view of the results presented in Example 3, discussed above. Applicants submit that the exemplified removal of an O-glycan with a terminal galactose residue provides sufficient enabling disclosure for the same or similar modifications that would be expected from the use of any enzyme capable of removing the non-sialylated O-linked carbohydrate comprising a terminal galactose residue, as recited in independent claim 16. For example, any galactosidase or endo-acetylgalactosaminidase, as recited in claim 18, would produce the same result insofar as it applies to enhancing the blood circulatory half-life of the modified glycoprotein. Thus, the skilled artisan could readily perform the full scope of the invention recited in claim 16 without undue experimentation in a manner similar to that discussed above with regard to the sialyltransferases. Accordingly, the full scope of the invention recited in independent claim 16 is enabled by the specification.

Other Effects of the Modified Glycoproteins are Not Claimed

Neither independent claim 1, nor independent claim 16, nor independent claim 25 requires any specific activity of the human C1 inhibitor apart from its extended circulatory half-life. Therefore, whether the carbohydrate modifying enzymes (*e.g.*, a sialyltransferase, a galactosidase, or an endo-acetylgalactosaminidase) produce any other effect, as asserted by the Examiner, is of no consequence to the presently claimed invention. The foregoing notwithstanding, Applicants direct the Examiner's attention to Example 1, paragraph 0027, and Example 4, paragraph 0038 of the specification, which indicate that sialylation (as recited in claims 1 and 25) or removal of an O-linked carbohydrate (as recited in claim 16) having a terminal galactose residue did not effect the protease activity of the modified protein, nor did it result in aggregation or degradation of the modified glycoprotein. This demonstrates that at least the stability and functional characteristics of the exemplified protein remained intact following the carbohydrate modifications recited in the presently claimed invention. Applicants submit that nothing more is required by the presently claimed invention.

Each of the dependent claims are enabled for at least the same reasons discussed above. Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

Claim Rejections - 35 U.S.C. §103

Claims 1-10, 13 and 16-22 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over **Paulson** *et al.*, WO 98/31826, **Schoenberger** *et al.*, *FEBS* 314: 430-434 (1992), and **Wolff** *et al.*, *Protein Expression and Purification* 22: 414-421 (2001) in view of **Glaser** *et al.*, WO 92/03149, and **Lamark** *et al.*, *Protein Expression and Purification*, 22:349-358 (2001).

As discussed with the undersigned on October 8, 2009, the Examiner appears to have inadvertently attributed a discussion of a recombinant human C1 inhibitor to the Paulson reference (*see* p. 7, 1st paragraph of the Office Action in which reference is made to a "p. 420, col. 1"), when, in fact, no such discussion or citation is present in Paulson. This attribution appears to be the basis of the 103(a) rejection of the claims and the response to Applicants arguments of July 7, 2008, as set forth on pages 6-8 of the present Office Action. In view of the

foregoing, Applicants respectfully request reconsideration of this rejection on the basis of the following remarks.

Claims 1, 4, 6-9, 13 and 25-27

Independent claims 1 and 25 are directed to a recombinant human C1 inhibitor, and to a method for modifying a recombinant human C1 inhibitor, respectively, wherein the plasma circulatory half-life of the protein has been extended via sialylation of a terminal galactose residue of an O-linked carbohydrate.

As discussed above, Paulson makes no reference to recombinant human C1 inhibitor. Furthermore, Paulson indicates that the circulatory lifetime of glycoproteins in the blood is highly dependent on the composition and structure of its *N-linked* carbohydrate groups. *See* p. 1, lines 16-17 of Paulson. The Examiner has acknowledged that Paulson does not teach the importance of O-linked glycosylation to the circulatory half-life of the protein. *See* paragraph bridging p. 7-8 of the April 19, 2006 Office Action. Thus, there is no recognition in the art that sialylation of O-linked carbohydrates affects circulatory half-life, and there is, therefore, no motivation to use the methods discussed in Paulson to sialylate O-linked carbohydrates on recombinant human C1 inhibitor to enhance plasma circulatory half-life, as presently claimed in independent claims 1 and 25.

None of the other references cited by the Examiner account for this deficiency of Paulson. Schoenberger discusses the removal of sialic acid from a C1 inhibitor (*see* p. 431, col. 2, 1st full paragraph), rather than sialylation, and neither Wolff, nor Glaser, nor Lamark discusses sialylation or plasma circulatory half-life. Thus, it would not have been obvious to a skilled artisan, based on these references, that sialylation of O-linked carbohydrates in a recombinant human C1 inhibitor would extend the plasma circulatory half-life of the protein, and the claimed invention recited in independent claims 1 and 25 is patentable over the cited art.

Each of the dependent claims is patentable over the cited references for at least the same reasons discussed above. Accordingly, Applicants respectfully request withdrawal of this ground of rejection as it applies to claims 1, 4, 6-9 and 13, and new claims 25-27.

Claims 16, 17, 19, 20 and 22-24

Independent claim 16 is directed to a method of extending the blood circulatory half-life of a glycoprotein by removal of a non-sialylated O-linked carbohydrate comprising a terminal galactose residue via *in vitro* incubation of the glycoprotein with an enzyme capable of removing the carbohydrate.

None of the cited references discusses the removal of non-sialylated O-linked carbohydrates via *in vitro* incubation with an enzyme, and none recognizes that the removal of such O-linked carbohydrates can be used to extend the blood circulartory half-life of a glycoprotein or glycoprotein containing compound, as recited in claim 16. These features of the claimed invention are absent from the cited references and the Examiner has provided no rationale by which a skilled artisan would have been motivated to modify the art to arrive at the invention recited in independent claim 16. Thus, a *prima facie* case of obviousness has not been established.

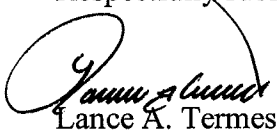
Paulson does not discuss removal of non-sialylated carbohydrates in any capacity, and, as discussed above, indicates that the circulatory lifetime of glycoproteins in the blood is highly dependent on the composition and structure of its *N-linked* carbohydrate groups. *Supra.* Schoenberger discusses the removal of sialic acid from a C1 inhibitor (*supra*), but makes no reference to the removal of *non-sialylated* carbohydrates. Wolff reports the removal of O-glycans from the C1 inhibitor for analysis of the presence of O-glycan chains, but removal of the O-glycans is performed by contacting the C1 inhibitor with lithium hydroxide (*see* paragraph bridging pp. 416-417), and there is no discussion of extending blood circulatory half-life by making such modifications. Glaser reports increasing circulatory half-life of a thrombomodulin analog by removing all or most of the sugar moieties in the 6 EGF-like domains (*see* p. 4, lines 35-38), which Glaser identifies as *distinct from the O-linked glycosylation domain. See* p. 11, lines 33-34. Moreover, there is no indication that the carbohydrates reportedly removed in Glaser are non-sialylated carbohydrates, as recited in the method of claim 16. Finally, Lamark reports that glycosylation does not appear to be important to the function of C1 inhibitor (*see* abstract and p. 357, penultimate paragraph) since a non-glycosylated C1 inhibitor produced by *E.*

coli had an active serpin domain, which ordinarily comprises three N-linked carbohydrate groups. *Id.* Lamark does not discuss removal of non-sialylated O-linked carbohydrates or corresponding changes to blood circulatory half-life.

In view of the foregoing, independent claim 16 is patentable over the cited art. Each of the dependent claims is patentable over the cited references for at least the same reasons discussed above. Accordingly, Applicants respectfully request withdrawal of this ground of rejection as it applies to claims 16, 17, 19, 20 and 22, and new claims 23 and 24.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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